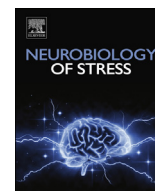


Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

Neurobiology of Stress

journal homepage: <http://www.journals.elsevier.com/neurobiology-of-stress/>

Untangling the Gordian knot of HIV, stress, and cognitive impairment

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ARTICLE INFO

Article history:

Received 20 November 2015

Received in revised form

4 February 2016

Accepted 9 February 2016

Available online 11 February 2016

Keywords:

HIV

Stress

Inflammation

CD4

Cognition

ABSTRACT

As individuals live longer with HIV, this “graying of the HIV epidemic” has introduced a new set of challenges including a growing number of age and inflammation-related diseases such as cardiovascular disease, type II diabetes, cancer, and dementia. The biological underpinnings of these complex and comorbid diseases are not fully understood and become very difficult to disentangle in the context of HIV and aging. In the current review we examine the contributions and interactions of HIV, stress, and cognitive impairment and query the extent to which inflammation is the linchpin in these dynamic interactions. Given the inter-relatedness of stress, inflammatory mechanisms, HIV, and cognitive impairment, future work will either need to address multiple dimensions simultaneously or embrace the philosophy that breaking the aberrant cycle at any one point will subsequently remedy the other related systems and processes. Such a single-point intervention may be effective in early disease states, but after perpetuation of an aberrant cycle, adaptations in an attempt to internally resolve the issue will likely lead to the need for multifaceted interventions. Acknowledging that HIV, inflammation, and stress may interact with one another and collectively impact cognitive ability is an important step in fully understanding an individual's complete clinical picture and moving towards personalized medicine.

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Abbreviation: IL-1 β , Interleukin-1 β ; IL-2, Interleukin-2; IL-6, Interleukin-6; IL-12, Interleukin-12; IL-18, Interleukin-18; ACTH, Adrenocorticotrophic hormone; AIDS, Acquired immune deficiency syndrome; ANI, Asymptomatic neurocognitive impairment; ART, Antiretroviral therapy; CBSM, Cognitive behavioral stress management; CNS, Central Nervous System; CRP, C-reactive protein; GALT, Gut-associated lymphoid tissue; GR, Glucocorticoid receptor; HAD, HIV-associated dementia; HANA, HIV-associated, Non-AIDS; HAND, HIV-associated neurocognitive disorders; HPA, Hypothalamic–Pituitary Adrenal; HRV, Heart rate variability; hsCRP, High-sensitivity C-reactive protein; INSTIs, Integrase strand transfer inhibitors; LPS, Lipopolysaccharide; LTP, Long-term potentiation; MND, Mild neurocognitive disorder; NNRTIs, Non-nucleoside reverse transcriptase inhibitors; NRTIs, Nucleoside reverse transcriptase inhibitors; PFC, Prefrontal cortex; PLWH, People living with HIV; PIs, Protease inhibitors; PTSD, Posttraumatic stress disorder; ROS, Reactive oxygen species; TNF α , Tumor necrosis factor alpha; Vpr, Viral protein r; WIHS, Women's Interagency HIV Study.

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<http://dx.doi.org/10.1016/j.jynstr.2016.02.005>

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1. Introduction

With increasing efficacy of antiretroviral therapy (ART), HIV has shifted from a disease with high mortality to a chronic disease with substantial longevity. By 2015, over half of people living with HIV (PLWH) will be aged 50 or older. This increase in age among those living with HIV has been referred to as the “graying of the HIV epidemic” and has introduced a new set of challenges including a growing number of age and inflammation-related diseases such as cardiovascular disease, type II diabetes, cancer, and dementia (High et al., 2012). The contribution of persistent immune activation and inflammation to HIV-associated, Non-AIDS (HANA) conditions in PLWH who are on adequate ART (Hunt, 2012) has garnered increased attention as these may fuel neurocognitive complications of the disease (Hong and Banks, 2015) which hinder daily functioning (Heaton et al., 2004). Despite the well-established inflammatory consequences of HIV, the perpetuating force behind sustained inflammation in otherwise healthy PLWH has not been identified. While the cellular and molecular mechanisms underlying the interaction between residual immune activation/inflammation and residual neurological disease are not well defined, a robust literature demonstrates a substantial impact of stress exposure on inflammation, immune activation, and cognitive function. Furthermore, HIV appears to interact with or accelerate age-related inflammation (Zapata and Shaw, 2014) leading to an exaggerated impact on both somatic systems (e.g., cardiovascular disease) and the central nervous system (CNS; e.g., neurocognitive impairment), which may produce a feed-forward cycle (Nemeth et al., 2014).

The interactions of stress with chronic complex disease states and aging generate a mechanistic quagmire making it difficult to isolate, study, and develop an understanding of the underlying pathology. Such stalemates halt treatment advances and conjure images of the legendary Gordian knot from Greek mythology. In this ancient story, King Gordius of Phrygia tied a complicated knot, which no one could make loose, until Alexander the Great cut it with his sword. Instead of disentangling the individual pieces of the problem, the only possible solution was to attack the gestalt condition. Although HIV, stress, and cognitive impairment have been studied, just like the Gordian knot, their interconnectedness has created a clinical problem in which teasing out what mechanisms contribute to the pathophysiology present is fraught with difficulty. Here we discuss what is known about this “Gordian knot” and debate the question of whether the best path forward is the study of the whole interconnected condition or continued attempts to isolate the individual components. We also evaluate the converging mechanism of inflammation, which may be driving the relationship between these three intertwined conditions. What is the best path forward to develop appropriate therapies to address the co-morbid and overlapping neuropathology of HIV, stress, and cognitive impairment with the added complexity of aging?

2. Main characters: biology of HIV infection

Although no longer in the spotlight of the world media, new HIV infections remain rampant, with 50,000 newly diagnosed people

per year in the United States and 2.3 million people diagnosed world-wide each year (Committee on Review Data Systems for Monitoring and Institute of, 2012). Fortunately, the advent of ART dramatically reduced acquired immune deficiency syndrome (AIDS)-related mortality, such that approximately 30 million people currently live with HIV around the globe (Hallett et al., 2014).

HIV is a retrovirus that primarily exerts its influences on the activated CD4⁺ T lymphocytes of the immune system. CD4⁺ T lymphocytes are known as “helper T-cells”; they are responsible for producing cytokines necessary for generating an appropriate and sufficient immune response for clearing pathogens. Although these are the primary cells infected in HIV, other cells with CD4 receptors also become infected, such as peripheral mononuclear cells and dendritic cells. After infecting a cell, the virus is rapidly replicated in the cells' nucleus; this process is dependent on reverse transcriptase, an enzyme that catalyzes the transcription of viral RNA into viral DNA that will then be integrated into the host cell's genome. During the initial infection, the viral load rises, and the hosts' immune system attempts to fight off the virus with a strong induction of inflammatory cytokines and chemokines. The viral load then decreases due to activation of the innate immune system and reaches a stable set point. Eventually, for reasons not yet understood, the virus is able to escape the control of the immune system, replication accelerates, and viral load increases. As viral load increases, more CD4⁺ T cells become activated and subsequently infected, ultimately leading to their death. Typically, the clinical severity of an HIV infection is determined by a patient's viral load and CD4⁺ T lymphocyte count. A clinical diagnosis of AIDS is garnered once the CD4⁺ T cell count falls below 200 cells/mm³. This diagnosis is reversible if ART is initiated and leads to reduction in viral load and a gradual increase in CD4⁺ T cells. If left unchecked, the accelerating destruction of the body's immune system facilitates entry and expansion of opportunistic infections, which can be fatal (Maartens et al., 2014).

HIV is treated using a combination of antiretroviral medications that fight the virus. These medications are categorized into one of six drug classes based on how they attack the virus. The first two drug classes, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs), block or disrupt reverse transcriptase or simply viral replication. The third drug class, protease inhibitors (PIs), blocks new/immature HIV from becoming a mature virus that can infect other CD4⁺ cells. Fusion inhibitors are the fourth drug class, and these drugs block the HIV envelope from fusing with the CD4 cell membrane. The fifth drug class is CCR5 antagonists (CCR5s) or entry inhibitors, and they block the C–C chemokine receptor type 5 (CCR5) co-receptor on the surface of CD4⁺ cells, which ultimately prevents HIV from entering the cell. Integrase strand transfer inhibitors (INSTIs), the last drug class, block the insertion of HIV DNA into CD4⁺ cell DNA. The guidelines state that ART is recommended for all PLWH to decrease the risk of disease progression. However, prolonged use of combinations of ART drugs can lead to drug resistance and, therefore, these treatments are often not prescribed until the first indication of immune suppression (Nath and Sacktor, 2006). Notably, despite the improvements in ART efficacy in terms of suppression of viral load, the incidence and prevalence of milder forms of HIV-

Associated Neurocognitive Disorders (HAND) have remained stable and may have even increased among asymptomatic HIV-infected individuals (Grant, 2008).

3. Setting the stage: interactions of HIV, stress, and cognition

The new complexity presented by increased life expectancy following HIV infection is the influence of HIV on normal aging processes. Aging with HIV appears to create a synergistic state with heightened co-morbidities including cardiovascular disease and depression which may contribute to neurocognitive impairment (Nemeth et al., 2014). Furthermore, despite the availability of ART, PLWH are not uniformly responsive to treatment (Moniz et al., 2014), and poor adherence is a primary factor in suboptimal treatment response (Li et al., 2014). Stress, emotional reactivity, and avoidant coping behaviors contribute to HIV progression through increases in nonadherence (Martinez et al., 2012). Additionally, aging-associated complexities may exacerbate the effects of stress on nonadherence in PLWH aged 50 and older (Halkitis et al., 2014; Warren-Jeanpiere et al., 2014; Wu et al., 2014). Notably, cognitive functioning is a predictor of medication management and non-adherence (Wagner, 2002; Hinkin et al., 2004), and the strength of the predictive capacity increases with age (Frain et al., 2014).

A strong relationship exists between psychosocial factors such as stress and adverse biological outcomes in PLWH (Sledjeski et al., 2005; Leserman, 2008; Fumaz et al., 2012; Brumsey et al., 2013); however, a critical gap subsists in our understanding of the mechanisms responsible for the adverse consequences of stress in the context of HIV infection. Available evidence from human investigation suggests that biological factors secondary to psychosocial exposures may drive the tempo of HIV pathogenesis (Sledjeski et al., 2005; Leserman, 2008; Fumaz et al., 2012; Brumsey et al., 2013) and contribute to variability in response to ART (Martinez et al., 2002; Sledjeski et al., 2005; Mugavero et al., 2009). For example, depressive symptoms are associated with a greater decline in CD4+ T-cell count and increased risk of AIDS mortality (Leserman, 2008). In addition, with the marked progress towards effective cure strategies for HIV (Thornhill et al., 2015), attention must be given to the potential impact of stress-related alterations in physiology on viral reservoir establishment and maintenance. Given the profound effects of stress on HIV pathogenesis (Capitanio et al., 2008; Chida and Vedhara, 2009) and treatment response (Leserman, 2008; Fumaz et al., 2012), it is not unreasonable to surmise that HIV-co-morbidities such as cardiovascular disease, neurocognitive complications, osteoporosis, liver disease, and kidney disease (Freiberg et al., 2013) may also be compounded by stress.

Despite substantive decreases in HIV-associated morbidity and mortality following the introduction of ART, neurocognitive complications of the disease remain high (Heaton et al., 1995; White et al., 1995; Sacktor et al., 2002; Giancola et al., 2006; Tozzi et al., 2007; Heaton et al., 2011). Specifically, the frequency of the two less severe HAND classifications, asymptomatic neurocognitive impairment and HIV-associated mild neurocognitive disorder, is high, at 44% (Heaton et al., 2010). Characterization has changed in the post-ART era such that the cognitive domains most impaired by HIV shifted from motor skills, cognitive speed, and verbal fluency to learning and executive function impairment (Heaton et al., 2011). An understanding of complex mechanisms underlying HAND, including the interactive effects of HIV pathogenesis and aging on cognition, will be critical in the coming decades as the lifespan of PLWH expands and the proportion living over the age of 50 rises dramatically (Deuffic-Burban et al., 2007; Vance et al., 2014).

Among HIV-infected men, increased age (i.e., over 50) is a significant risk factor for HIV-associated dementia (HAD) (Valcour

et al., 2004). By contrast, there is relatively little known about HAND in HIV-infected women, though HIV-infected women may be at increased risk for cognitive decline due to the high prevalence of psychosocial and mental health problems, substance abuse, lower cognitive reserve due to lower education and pre-morbid intelligence (Maki and Martin-Thormeyer, 2009), and increasing age (Basso and Bornstein, 2000; Farinpour et al., 2003). From 1988 to 1997, only 9.3% of research participants in HIV-related neurocognitive studies were female (Fox-Tierney et al., 1999). Although few studies had sufficient numbers of women to assess neurocognitive complications of HIV, rates of cognitive impairment within smaller samples of women in the Women's Interagency HIV Study (WIHS) were high (42%) (Richardson et al., 2002). Important new data from a landmark study (Cysique and Becker, 2015; Maki et al., 2015) in the WIHS revealed that the cognitive domains impacted in women living with HIV are distinct from those impacted in HIV-infected men (Heaton et al., 1995, 2011). Although HIV-infected women did not show significant neurocognitive impairment on commonly used measures of executive function, including the Stroop Trial 3 and Trail Making Test Part B, complex attention, and learning, women living with HIV demonstrated profound deficits in verbal memory and simple measures of attention/concentration (Maki et al., 2009). Consistent with these epidemiological findings, neuroimaging findings in the WIHS also link hippocampal functioning to verbal memory deficits in HIV-infected women (Maki et al., 2009). Notably, across multiple studies certain factors have been identified that are differentially associated with verbal learning and memory impairments in HIV-infected women compared to HIV-uninfected women, including anxiety and perceived stress (Rubin et al., 2014, 2015a). Post-traumatic stress is also related to impaired verbal learning and memory, particularly in HIV-infected women with a history of sexual abuse and/or physical violence (Rubin et al., 2015c). The stress-related memory deficits may be partially accounted for by prefrontal cortical atrophy in HIV-infected women (Maki et al., 2009; Rubin et al., 2015b). To date, the data collectively suggest that the neurobiological underpinnings of cognitive deficits diverge between men and women and that stress may serve as a more salient trigger in women.

4. Inflammation as the director

As discussed in subsequent sections, the immune system appears to be the primary connection between HIV, stress, and cognition. Upon HIV infection, numerous cytokines, such as interleukin-2 (IL-2) and interleukin-6 (IL-6) are produced and an inflammatory state is established. These specific cytokines lead to glucocorticoid resistance, causing an elevated basal level of cortisol in PLWH. This increase in basal cortisol concentrations, compared to healthy controls, and the elevated presence of cytokines are hypothesized to contribute to HIV-infected individuals' susceptibility to mood and anxiety disorders as well as cognitive disorders both individually (Seilhean et al., 1997; Rostasy et al., 2000; Tiraboschi et al., 2015) and through interactions among the governing systems (Snyder, 2013; Scott et al., 2015). Thus, the inflammatory response may be the key in understanding how stress, HIV, and aging synergize.

4.1. HIV and inflammation

The advent of readily available ART has unveiled HIV-related complications independent of viral replication. One of the current focuses of HIV research is the constant inflammation throughout the infection. IL-6 is a cytokine that mediates a strong pro-inflammatory systemic response. Middle to older adults (45–76

years of age) on combination ART were found to have 40–60% higher concentrations of IL-6 in circulation compared to age-matched controls (Neuhaus et al., 2010). The same study by Neuhaus et al. (2010) also found that PLWH had an increased amount of high sensitivity C-reactive protein (hsCRP) in circulation, another clinically significant indicator of systemic inflammation. Additionally, PLWH on ART have been shown to have persistent T-cell activation despite adequate reduction of viral replication (Hunt et al., 2003). Elevation of IL-6, hsCRP, and T-cell activation all suggest a systemic state of high inflammation during HIV despite ART (Deeks et al., 2013).

One of the hypotheses regarding systemic inflammation due to HIV infection suggests the gut mucosa is the main source of inflammation. The epithelial mucosa of the gut contains the gut-associated lymphoid tissue (GALT), home to many HIV-susceptible CD4+ T cells (Brenchley et al., 2004; Mehndru et al., 2004). Direct infection of lymphocytes in the gut leads to epithelial injury. Loss of integrity in the gut mucosal layer leads to chronic exposure to microbial products, such as lipopolysaccharide (LPS) found on the outer membrane of *E. Coli* common to the digestive tract, contributing to systemic inflammation (Brenchley et al., 2004).

Not only are PLWH in a chronic state of inflammation, but they are also in a state of hypercoagulability, reflected by an increased D-dimer level (Neuhaus et al., 2010). The evidence of increased inflammation and hypercoagulability in PLWH seem to offer an explanation as to why they are more likely to suffer from cardiovascular disease (i.e. myocardial infarction and ischemic heart disease) (Obel et al., 2007; Triant et al., 2007; Nordell et al., 2014). It is important to emphasize that this state of inflammation in PLWH is independent of viral load (Ronsholt et al., 2013). Although combined ART initially lowers systemic tumor necrosis factor alpha (TNF α) (Aukrust et al., 1999), another cytokine important for inflammatory response, TNF α levels recover and can increase beyond initial levels, remaining elevated compared to controls even after 12 years of ART (Ronsholt et al., 2013). This further demonstrates that while established ART regimens can suppress viral load, they cannot suppress inflammation associated with HIV infection. The source of this ongoing inflammation is a current area of study and a barrier to curing HIV because activated T cells are easily infected, such that any interruption in ART will result in viral replication due to the primed T cells. Further, HIV-associated inflammation is hypothesized to be the cause of non-AIDS HIV-co-morbidities such as cardiovascular disease, cancer, and neuropsychiatric disorders.

4.2. Stress, HIV, and inflammation

The degree of inflammation present in PLWH may be correlated to psychological stress. A strong correlation exists between IL-6 and psychological stress as well as mood and anxiety disorders (Fumaz et al., 2012). PLWH have a higher rate of current and lifetime major depression, which can be precipitated by chronic stress, compared to the general population (Atkinson and Grant, 1994; Dew et al., 1997). Additionally, post-traumatic stress disorder (PTSD) has a greater prevalence amongst HIV-infected individuals with a range of 5–74% compared with 7–10% prevalence in the general population (Sherr et al., 2011). Anxiety and depression appear to be associated with the symptomatology (fever, persistent diarrhea, night sweats, thrush, shingles, upper respiratory infections, fatigue, lymphadenopathy, and muscle joint pain) of the virus versus the degree of immunodeficiency (Penedo et al., 2003b) and are more prevalent in women than men (Brief et al., 2004; Robertson et al., 2014). Furthermore, cognitive behavioral stress management (CBSM) intervention in PLWH has been shown to decrease reported distress (Schneiderman, 1999), as well as self-reported levels of

anxiety, depression, anger, and confusion (Antoni et al., 2000a, 2000b). This form of stress management also helps to reduce physiologic reports of stress as measured by reduced cortisol urine output (Antoni et al., 2000a, 2000b). Inability to effectively cope with stress has been correlated with poorer outcomes of psychological distress and maladjustment to HIV infection (Grassi et al., 1998). Individuals with maladaptive techniques for coping with stress, such as illicit substance use and avoidance, have greater psychological distress than patients who cope using methods such as positive reframing and acceptance (Lutgendorf et al., 1998; Penedo et al., 2003a, 2003b). Collectively, these and other studies, demonstrate a strong association between stress and HIV.

Acute stress has been shown to lead to increases in peripheral inflammation. Across studies, circulating IL-6 and interleukin-1 β (IL-1 β) appear to be the most consistently increased following exposure to acute stress (Stephens et al., 2007). Increases in inflammatory markers in the periphery occur gradually, reaching a peak concentration at 2-h after the stress has been present (Rohleder, 2014). The level of inflammation caused by acute stress typically depends on a variety of additional factors, such as: level of fitness, self-esteem, depressive mood, and loneliness. It has been suggested that the inflammation due to stress may be mediated by the sympathetic nervous system (Kop et al., 2008). However, the specific mechanism as to how acute stress promotes an increase in peripheral inflammatory markers is unknown.

Chronic stress also leads to an increase in inflammation. One inflammatory marker that increases with exposure to chronic stress is TNF- α , which acts downstream to increase oxidative stress, causing cellular damage (Munhoz et al., 2004). Chronic stress also promotes infiltration of lymphocytes in the small intestine, which then may lead to other health complications, such as obesity (Lee, 2013). Similarly to acute stress, chronic stress has been demonstrated to increase the peripheral inflammatory cytokine IL-6 (Kiecolt-Glaser et al., 2003), as well as C-reactive protein (CRP) (Rohleder et al., 2009). A current proposed mechanism to explain the increase in inflammatory markers with chronic stress is glucocorticoid resistance (Rohleder, 2012). Chronic stress decreases the levels of glucocorticoid receptors (GR) in the brain, and without these receptors, glucocorticoids cannot exert their anti-inflammatory effects (discussed in depth below).

Not only does acute stress promote inflammation in the periphery, but the CNS also experiences inflammation following exposure to stress. Acute stress promotes microglial activation in regions of the brain, including the thalamus, hypothalamus, hippocampus, substantia nigra, and central gray (Sugama et al., 2007). Interleukin-18 (IL-18) appears to be a cytokine necessary for the activation of microglia during stress (Sugama et al., 2007). Similarly, chronic stress can enhance the activation of microglia following a pro-inflammatory stimulus in the CNS (de Pablos et al., 2014). Treatment with a GR antagonist abolishes the synergistic activation of microglia following stress and a pro-inflammatory stimulus, suggesting that the receptor mediates the effects of chronic stress on the immune system (de Pablos et al., 2014). Though acute and chronic stress may increase inflammation in the nervous system through different mechanisms, it is important to note they both result in the activation of microglia. Despite the role of microglia in protecting the nervous system, when activated, they release pro-inflammatory and cytotoxic factors, which can lead to neuronal death (Kim et al., 2000; de Pablos et al., 2014).

4.3. Cognitive impairment, HIV, and inflammation

Neurocognitive deficits are a common feature of HIV/AIDS, and the frequency and severity of these deficits increase as the disease progresses. Notably, neurocognitive impairment diminishes quality

of life and presents an economic challenge for PLWH, their social support systems, and the larger community. The cognitive deficits associated with HAND range from subtle cognitive deficits to marked dementia syndrome referred to as HIV-associated dementia (HAD) (Heaton et al., 2011). HAND is categorized into three levels depending on the number of cognitive domains impaired and the level of interference in everyday functioning. These three levels include asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HAD. A diagnosis of HAND (least severe level, ANI) requires impairment in at least two cognitive domains as indicated by performance of at least 1.0 standard deviation below the mean for age and education appropriate norms on standardized neuropsychological tests. A diagnosis of MND additionally requires that the cognitive impairment mildly interfere with daily functioning (self-reported or observation by knowledgeable other in work, homemaking, or social functioning). HAD classification requires marked cognitive impairment (2.0 standard deviations below standardized neuropsychological test norms) and significant impairment in daily functioning. For a proper diagnosis of HAND, all other etiologies explaining the cognitive disturbance must be ruled out.

HIV viral proteins that are able to cross the blood brain barrier can lead to the production of cytokines in the neurovascular endothelium, leading to neuroinflammation (Dohgu et al., 2011). As mentioned previously, HAND is the primary neurocognitive disorder in PLWH, which is most likely due to the high levels of neuroinflammation present. IL-6 levels are increased in the cerebrospinal fluid of individuals diagnosed with HAND, and remain increased 12 weeks after starting ART (Airolidi et al., 2012). Similar to the effects of stress on neuroinflammation, HIV exerts most of its neuroinflammatory effects through activation of monocytes that migrate into the CNS perivascularly. Typically, activated monocytes express a high level of CD14 on their surface, but a pro-inflammatory phenotype of monocytes with CD16 expression in addition to CD14 exists in about 10% of monocytes (Belge et al., 2002). This highly pro-inflammatory monocyte phenotype is increased in up to 40% of PLWH (Pulliam et al., 2004).

Though ART has been successful in keeping viral loads low, maintaining CD4⁺ T cell levels, and improving cognition in some cases (Suarez et al., 2001; Sacktor et al., 2009), it has not eliminated the neurocognitive complications of HIV infection. Prior to ART, the area most affected by inflammation is the basal ganglia. In the context of ART, the hippocampus, entorhinal cortex, and temporal cortex are the most affected by inflammation (Anthony and Bell, 2008). While there has been a significant drop in the rate of HAD with the advent of ART, rates of mild-to-moderate neurocognitive impairment remain high (Heaton et al., 2011). HIV-related cognitive deficits are believed to persist in the post-ART era for various reasons including poor penetration of the CNS, drug resistance, poor medication adherence, and astrocytes serving as viral reservoirs (Kramer-Hammerle et al., 2005; Cysique and Brew, 2009). The HIV virus penetrates the CNS in the early stages of disease (Clements et al., 2002) and once this occurs, the virus cannot be eliminated from infected microglia and astrocytes due to the long lifespan and low turnover of these infected cells (Nath and Sacktor, 2006). Many ART therapy medications are unable to effectively enter the CNS due to poor penetration of the blood brain barrier, and in some cases, the subtherapeutic levels of the drug that do enter can cause the development of resistant viruses (Ellis et al., 2000; Price and Deeks, 2004). Advances have been made in determining which drugs are most effective in penetration of the blood brain barrier (Best et al., 2011; Decloedt et al., 2015) and in some cases these diminish neuroinflammation (McComsey et al., 2012; Calza et al., 2016); however, neuropsychiatric and neurocognitive difficulties remain challenges for PLWH (Spudich, 2014).

Although there has been a decrease in HAD, the increase and persistence of HAND in the era of ART suggests that another mechanism aside from viral replication and infection is responsible for the neurocognitive deficits present in HIV. One working hypothesis regarding the mechanism for neurocognitive dysfunction in HIV is that HIV infection activates macrophages and microglia in the CNS, which then release cytotoxins, leading to neuronal and astrocyte injury (Kaul et al., 2001). It is important to note that HIV only infects microglia and macrophages; the virus does not infect neurons. The presence of macrophages and microglia has been shown to be more strongly correlated with HAD compared to the presence of HIV-1 virus (Glass et al., 1995). Once the microglia in the CNS become activated, they release inflammatory cytokines, chemokines, and excitotoxic substances (Lipton and Gendelman, 1995). All of these released substances may damage neurons, contributing to the pathology found in HAD (Glass et al., 1995). A potential intrinsic feature of HIV that leads to the activation of monocytes and microglia is the gp120 envelope protein (Lipton, 1992). Additionally, gp120 and pro-inflammatory cytokines can lead to the production of reactive oxygen species (ROS), which leads to damage of DNA and RNA. Higher levels of ROS have been observed in the CNS of HIV patients with HAND compared to control HIV patients without HAND as well as control non-infected patients (Zhang et al., 2012). Thus, even with the maintenance of normal CD4⁺ T cells and lower viral count with ART, the gp120 protein that is also expressed in infected cells will contribute to the activation of macrophages and monocytes in the CNS, leading to cell death and ultimately neurocognitive deficits.

5. Supporting cast: mechanisms linking HIV, stress, and cognitive impairment

5.1. Sympathetic nervous system

When an individual is under stress, the autonomic nervous system activates its sympathetic branch to release norepinephrine and epinephrine. Norepinephrine and epinephrine work on their target organs to produce a wide range of physiologic effects, such as increasing heart rate, stimulate sweat secretion, and dilation of bronchioles. Studies on psychological stress on the autonomic nervous system focus on heart rate variability (HRV) as an indicator of autonomic nervous system dysfunction. Furthermore, these particular studies typically focus on work-related stress as a model of chronic psychological stress. These stress studies have demonstrated that workplace stressors lead to a decrease in parasympathetic nervous system's effect on the heart; leading to an imbalance with the sympathetic nervous system primarily affecting the heart rate (Jarczok et al., 2013). Thus, chronic psychological stress leads to an imbalance of the two components of the autonomic nervous system: the sympathetic nervous system and parasympathetic nervous system. Such dysregulation of the autonomic nervous system from chronic stress can have significant effects on an individual's health, specifically in regard to cardiovascular disease; a decrease in parasympathetic-mediated HRV is associated with an increased risk of cardiovascular disease (Thayer et al., 2010).

Additionally, the autonomic nervous system has been demonstrated to affect the immune system (Severn et al., 1992; Hasko et al., 1995; Elenkov et al., 2000). Upon treating mice with an alpha 2 adrenoreceptor antagonist prior to LPS injection, plasma levels of TNF- α were decreased while IL-6 levels were increased compared to non-treated animal controls (Hasko et al., 1995). Furthermore, epinephrine and a beta-adrenergic agonist prevented the production of TNF- α following LPS stimulation in human blood samples (Severn et al., 1992). Beta-adrenergic agonists have also

been demonstrated to inhibit IL-18 and IL-12 production in human peripheral blood mononuclear cells following LPS stimulation (Mizuno et al., 2005). Together, these studies suggest that the autonomic nervous system plays a modulatory role on the immune system and inflammation.

Autonomic nervous system dysfunction has been demonstrated as a neurologic complication of HIV infection (Craddock et al., 1987) and in individuals whose HIV status progresses to AIDS (Becker et al., 1997). In a cohort of 102 PLWH, 61% of individuals demonstrated autonomic dysfunction with a score greater than 3 on the composite autonomic severity score (Robinson-Papp et al., 2013). Similarly, individuals whose HIV status progresses to AIDS demonstrate a reduction in HRV (Becker et al., 1997), an effect similar to the reduction in HRV as a result of chronic psychological stress. Notably, ART usage significantly reduces the occurrence of autonomic dysfunction (Correia et al., 2006). However, in individuals on ART, the level of viral suppression does not affect the occurrence of autonomic dysfunction. PLWH on ART with an undetectable HIV viral load have the same occurrence of autonomic dysfunction as individuals on ART with a detectable load (Chow et al., 2011). Despite the strong evidence of autonomic dysfunction associated with HIV infection, the mechanism behind the pathogenesis is unknown.

5.2. Hypothalamic–pituitary–adrenal (HPA) axis

In addition to the sympathetic response to stress, the HPA axis serves as the second mediator of the body's response to a stressor. The end point of this endocrine pathway is for cortisol to be released by the adrenal cortex. Once cortisol binds to GR, a transcription factor, the receptor allows for a multitude of downstream effects, including gluconeogenesis, metabolism of fat, protein and carbohydrates, and suppression of the immune system. Cortisol exerts a negative feedback effect on receptors in the hypothalamus and pituitary to stop its own production. Cortisol also influences other brain regions including the hippocampus and prefrontal cortex (PFC), which are critical to cognitive functioning, particularly to verbal memory performance (Buckner et al., 2000; Dickerson and Eichenbaum, 2010).

Although the HPA axis is efficient in handling acute stress, chronic stress may cause long-term changes in the axis. In various human and animal studies, chronic exposure to stress has been demonstrated to increase the basal levels of cortisol, as well as secretion levels in response to acute stress (Lupien et al., 2009). The primary hypothesis to explain this increase in basal cortisol suggests that down-regulation of glucocorticoid receptors or reduced sensitivity of the receptors leads to a disruption in negative feedback. This hypothesis will be further explained later on.

Studies have shown HIV-infected individuals, predominately men, have higher cortisol levels compared to non-infected controls (Membreno et al., 1987; Chrousos and Zapanti, 2014). Other steroids produced by the adrenal glands, such as corticosterone, deoxycorticosterone, and 18-hydroxycorticosterone remain at levels similar to those in non-infected controls (Membreno et al., 1987). Despite these normal levels in PLWH, administration of cosyntropin, a synthetic derivative of adrenocorticotrophic hormone (ACTH), does not cause the same magnitude of increase seen in HIV-uninfected individuals (Membreno et al., 1987). This suggests that alterations in the pathway occur due to actions of HIV infection.

One of the theories regarding HIV's effect on the HPA axis focuses on cytokine signaling leading to stimulation of target organs in the hormone pathway. As discussed earlier, HIV leads to elevation of circulating inflammatory cytokines. One specific cytokine implicated in the pathogenesis of HPA dysfunction in the context of

HIV is interleukin-1 (IL-1). IL-1 has the ability to stimulate the hypothalamus and cause the secretion of corticotropin-releasing hormone (CRH) (Bernton et al., 1987; Sapolsky et al., 1987), which will lead to downstream activation of the HPA axis and eventual cortisol release. Alternatively, it has also been suggested that a key protein on the viral coat, gp120, may mediate the increase in CRH, rather than mechanisms directly through the immune system (Costa et al., 2000). Not only does IL-1 stimulate the HPA axis, but two other key cytokines mediate a similar response including IL-6 and TNF- α . Both of these cytokines help to mediate an increase in plasma levels of ACTH (Perlstein et al., 1993). As discussed earlier, there is systemic inflammation present in patients regardless of successful ART; this systemic inflammation leads to increases in IL-6 and TNF- α , promoting the stimulation of ACTH secretion and eventual elevated levels of cortisol.

Although the specific mechanism remains to be elucidated, it can be said that infection with HIV leads to alterations in the HPA axis, causing an observable increase in cortisol secretion levels. Even if this pathology is due to stimulation of the pathway through cytokines versus gp120 on the HIV viral coat, successful ART cannot prevent HPA axis dysfunction. Both HIV and stress lead to increased basal cortisol secretion; however, the mechanisms in which these two conditions cause a similar clinical phenomenon may be distinct. Where these two pathways converge to both produce elevated cortisol secretion will be better discussed with regard to the GR.

5.3. Glucocorticoid receptor

The GR mediates the effects of cortisol on its target organs. Once cortisol binds to the receptor, it translocates to the nucleus and serves as a transcription factor. Additionally, activation of the receptor contributes to negative feedback on the HPA axis. Chronic stress has been demonstrated to affect the expression of the GR by decreasing messenger RNA levels of the GR in specific brain regions, such as the hippocampus, cerebellum, and frontoparietal cortex (Herman et al., 1995; Kitraki et al., 1999). With lower levels of GR present in the brain, there is insufficient negative feedback, and cortisol levels are able to increase above normal physiological levels.

The increase in cortisol levels in a subset of individuals with HIV may be due to altered characteristics of the GR. These patients have elevated cortisol and ACTH, but peripherally appear to be in a hypocortisol state with weakness, weight loss, hypotension, and hyponatremia. This particular clinical picture of PLWH has been shown to be due to a reduced affinity of GR on mononuclear cells to its ligand, leading to a glucocorticoid-resistant state (Norbiato et al., 1992, 1998). Additionally, the lower affinity of GR leads to an increase in its expression in an attempt for compensation (Norbiato et al., 1992; Kino and Chrousos, 2004). The inflammatory state intrinsically present in HIV infection may also cause the decreased affinity of GRs, and thus the glucocorticoid-resistant state. The combined presence of IL-2 and interleukin-4 (IL-4) has been shown to lead to the change in GR-binding affinity and increase in GR number in peripheral blood mononuclear cells (Kam et al., 1993). Alternatively, structural protein viral protein r (Vpr) of HIV has been implicated in potentiating GR signaling. Vpr acts as a co-activator of GR and may lead to glucocorticoid hypersensitivity (Kino and Chrousos, 2004).

Although stress and HIV infection have seemingly opposite effects on the GR, with stress decreasing its expression and HIV increasing it, the end result is similar in both situations. Both HIV and stress ultimately lead to a glucocorticoid-resistant state in which receptors are unable to transduce cortisol's signal to the nucleus and act as a transcription factor. The effect on the GR under

either influence appears to be what ultimately leads to significant changes in the HPA axis.

6. A twist in the plot: negative glucocorticoid effects independent of inflammation?

Glucocorticoids impact a broad range of systems, and not all deleterious effects of glucocorticoids are the indirect result of inflammation. Uncontrollable stress, chronic stress, and stress hormones also affect cognitive abilities reliant on the hippocampus and PFC. A clinical study by Lupien et al. (1998) sought to explore the relationship between cortisol and hippocampal volume, as well as the subsequent cognitive effects in non-HIV infected patients. They found that increased cortisol levels were associated with a reduction in hippocampal volume and impaired hippocampus-dependent memory. The same group also observed that declarative memory is impaired in elderly subjects upon exposure to a stressful condition (Lupien et al., 1997). More so, they found that the subjects who had the affected declarative memory, “responders”, had an earlier increase in cortisol prior to the stress event compared to “nonresponders”. These clinical studies demonstrate that stress affects cognition at the level of the hippocampus, leading to effected spatial and declarative memory. Pharmacological administration or suppression of glucocorticoids also affects performance on tasks dependent on the hippocampus (e.g., verbal memory) and/or PFC (e.g., verbal and working memory) (Lupien et al., 1999; Henckens et al., 2011; Terfehr et al., 2011a,b; Henckens et al., 2012).

Numerous rodent studies have observed that high levels of exposure to glucocorticoids lead to degeneration of the hippocampus, and ultimately spatial learning deficits (Landfield et al., 1981; Issa et al., 1990). In the PFC, chronic stress and corticosteroid-induced stress can cause dendritic shortening and atrophy (McEwen, 2007). Studies point to decreased synaptic plasticity as a potential mechanism for how stress affects the hippocampus (Diamond and Rose, 1994; Gerges et al., 2004; Zoladz et al., 2012). The specific pathway that appears to be affected is long-term potentiation (LTP), as evidenced by reduced levels of CaMKII. CaMKII is a serine/threonine-specific protein kinase that has been heavily implicated in LTP through promotion of dendritic spine and synapse formation. In these studies, decreased performance in a spatial memory task following exposure to stress was associated with lower CaMKII, especially its active phosphorylated form. However, it remains to be elucidated if the increased cortisol from stress causes the lower amounts of p-CaMKII or if some other mechanism present in chronic stress, such as increased inflammatory substrates, leads to the impaired LTP.

Further complicating the elucidation of the relationship between glucocorticoids and cognitive function is the divergence of impact between men and women. Cortisol has been shown to be negatively associated with cognition in women but not in men. For example, 12-h free cortisol excretion is associated with poorer delayed verbal recall in women but not men in a community based sample of older adults. Furthermore, women who showed longitudinal increases in cortisol over a 2.5-year period were more likely to show declines in memory compared with women who exhibited no increases in cortisol over time (Seeman et al., 1997). In a subsequent study, a sex difference was observed in that the effects following a psychosocial stressor such that cortisol levels correlated negatively with memory and not mental rotations in women but not men (Wolf et al., 1998). Finally, a similar effect was observed on the Wisconsin Card Sorting Task, a prefrontal task. Cortisol levels before test performance correlated negatively with performance in women and positively with performance in men (McCormick et al., 2007). Collectively, these data demonstrate a relationship between

stress/glucocorticoids and cognitive function, but they do not rule out the possibility of inflammatory mechanisms playing a role in the relationship because inflammatory markers were not assessed in the studies.

7. Can stress, cognitive impairment, and HIV be disentangled from each other, or from inflammation? Do they need to be?

Given the inter-relatedness of the stress, inflammatory mechanisms, HIV, and cognitive impairment, future work will either need to address classification of any two endpoints or embrace the philosophy that breaking the aberrant cycle at any one point will subsequently remedy the other related systems and processes. Such a single-point intervention may be effective in early disease states, but after perpetuation of an aberrant cycle, adaptations in an attempt to internally resolve the issue will likely lead to the need for multifaceted interventions.

Acknowledging that HIV, inflammation, and stress may interact with one another and collectively impact cognitive ability is an important step in fully understanding an individual's complete clinical picture. Looking to the future of personalized medicine, it is important to recognize that if the gestalt condition is not treated, the underlying system targeted should be tailored to the individual. For instance, if a PLWH has an extensive history of early life trauma, they are likely to have an exaggerated inflammatory response and a poorly responsive HPA axis (Neigh et al., 2009). If this person presents with cognitive impairment, it could be a result of the elevated inflammation, but that inflammation would be secondary to both the HIV infection and the physiological adaptations caused by early life stress. Although the clinical presentation may be similar to someone without the influence of early life stress, the underlying biological substrates would be divergent, which could impact the efficacy of any one treatment strategy across a diverse population of individuals. Although HIV is a robust virus, the influence of the host on the progression and presentation of co-morbidities of the infection should not be underestimated. This is clearly illustrated by the profound sex differences in HIV and cognition discussed above and echoed by the impact of aging on all systems of the body. Although further research is required to provide exact answers for how to best treat the co-occurrence of HIV, stress, and cognitive impairment, it is essential to raise awareness among both clinicians and researchers about these intertwined systems and the pervasive influence of inflammation across these domains.

Acknowledgments

This work was partially supported by funding from a 2015 HIV and Aging Pilot Award to G.N.N. (R24 AG044325 sponsored by Wake Forest University) and Emory University's CFAR (P30AI050409). G.N.N. also received support from K18MH105098 from the National Institute of Mental Health. L.H.R. was supported by 1K01MH098798-01 from the National Institute of Mental Health. The funders had no role in review design, data collection and analysis, decision to publish, or preparation of the manuscript.

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